(i.e., $f(e) = -30$ for $e \leq 10$, $= e-40$ for $10 < e < 40$, and $= 0$ for $e \geq 40$).

Thus, there was no dependence upon attained age, and constant ERR/Sv, at different levels, for exposure ages less than 10 and 40 or older, with a linear transition in the logarithmic scale between $e = 10$ and $e = 40$. Likelihood profile distributions for ERR/Sv were computed for $e = 10$, 20, 30, and 40, and interpolated for e between 10 and 40 (Table IV.D.9)

For non-melanoma skin cancers other than basal cell carcinoma, which is dominated by squamous cell carcinoma, the unmodified point estimate of ERR/Sv was negative and no convergent estimate could be obtained if an age-dependent modifying term was introduced with either a free or fixed parameter value. We therefore requested a single profile for ERR/Sv, with no modification by age (Table IV.D.9).

The Ron et al data set had only 10 cases of malignant melanoma, far below our inclusion criterion of 50 cases at doses greater than 5 mSv, and we therefore did not include that cancer type.

5. Radon-related lung cancer.

As mentioned above at the end of section IV.C, a 1996 report prepared for the Department of Justice (DOJ, 1996) contains tables of cumulative radon exposures, in working level months (wlm), consistent with point estimates and upper 80% and 90% confidence limits for probability of causation greater than or equal to 50%, and the original data set used for these calculations, but restricted to exposures ≤ 3200 wlm, was made available to the working group. The working group attempted to approximate Appendix Table 3a of the DOJ report, modeling ERR as follows:

$$\mathrm{ERR}(wlm,e,t) = \alpha\, wlm^{\beta} \exp\{\gamma f(a) + \delta g(t)\},$$

where *wlm* is cumulative radon exposure in working level months, a is age at diagnosis, t is time since last exposure, α, β, γ, and δ are unknown parameters, and

$$f(a) = \min[\max(a-45, 0), 30],$$

$$g(t) = \min[\max(t-5, 0), 20];$$

(i.e., $f(a) = 0$ for $a \leq 45$, $= a - 45$ for $45 < a \leq 75$, and $= 30$ for $a > 75$;

$g(t) = 0$ for $t \leq 5$, $= t - 5$ for $5 < t \leq 30$, and $= 20$ for $t > 25$).

Thus, ERR was assumed to be proportional to an unknown power of cumulative exposure in wlm, and to be constant in a (at different levels) for $a \leq 45$ and $a > 75$, and to be constant in t (again, at different levels) for $t \leq 5$ and $t > 25$. Likelihood functions for $\mathrm{ERR}_{1\,wlm}$ are given in Table IV.D.10 or smokers and non-smokers, for $a \leq 45$, $a = 69$, and $a > 75$, and for $t \leq 5$, $t = 15$, and $t > 25$, for interpolation in a and t. For ERR at arbitrary *wlm*, IREP multiplies $\mathrm{ERR}_{1\,wlm}$ by $wlm^{0.82}$.

E. Correction for random and systematic errors in A-bomb survivor dosimetry

Our treatment of random and systematic errors in A-bomb survivor dosimetry was based mainly on the treatment described in Chapter 3 of NCRP Report 126 (1997), and the reader is referred to this material for details. The NCRP approach was also used by the EPA (1999). Dosimetry for the A-bomb survivors is currently being re-evaluated (NAS/NRC, 2001). Revisions in dosimetry could change the estimated risk from gamma rays slightly and might also affect the shape of the dose-response function (Kellerer and Nekolla 1997; Pierce and Preston 2000). In the next year or two, it is expected that revised dose estimates will become available, that uncertainties in these estimates will be evaluated, and that analyses based on the revised doses will be conducted. Uncertainties resulting from systematic biases in A-bomb survivors will need to be reevaluated when these revisions become available. For now, the evaluation from NCRP 26 is used, and the uncertainties discussed below in 2), 3) and 4) should be considered as "place-holders" for a more appropriate evaluation. Changes in dosimetry should not greatly affect the random errors discussed in 1).

For each source of uncertainty, a bias factor with an uncertainty distribution was specified, and this factor was used to correct ERR estimates based on the A-bomb survivor data. Sources of bias and uncertainty that were evaluated by the NCRP are as follows:

1) Uncertainty in the magnitude of random errors in the doses of individual survivors, called R_E in NCRP Report 126, contributed differently to biased uncertainty for solid cancers and the leukemia, for which the forms of the dose response were linear and linear-quadratic, respectively. Unlike the NCRP report, the present report is concerned with individual cancer sites and must consider the two cases separately: uncertain bias correction factors $1+F_L(R_E)$ and $1+F_Q(R_E)$ for cancers with linear and linear-quadratic dose responses, respectively. Pierce et al (1990) recommended a lognormally-distributed random error in individual dose estimates with geometric mean (GM) = 1 and geometric standard deviation (GSD) = exp(0.35), corresponding to an upward correction in estimated risk of 9.0% for solid cancers and 5.6% for leukemia, with essentially no effect on the variability of the corrected risk estimates. There is, however, some uncertainty corresponding to the assumed GSD of the lognormally-distributed random error in dose estimates: the corresponding upward corrections are 6.8% and 4.3% for solid cancers and leukemia, respectively assuming log GSD = 0.30, and 11.4% and 7.2% assuming log GSD = 0.40. If we consider 0.30 and 0.40 to correspond to the 10th and 90th percentiles of an uncertainty distribution for log GSD, and consider that random error in dose assignment can only bias estimated risk downward, it seems appropriate to assume that $F_L(R_E)$ and $F_Q(R_E)$ are lognormal with GM=8.8% and 5.56%, respectively, with common GSD=1.22 (i.e., LN(8.8%, 1.22)) and LN(5.56%, 1.22)).

2) Uncertainty in the appropriate choice of neutron RBE in analyzing A-bomb survivor data,

denoted N_R in NCRP 126 with error factor $f(N_R)$ distributed according to a triangular distribution with minimum 0.9, most likely value 1.0, and maximum 1.1 (i.e., triangular(0.9, 1.0, 1.1)).

3) Uncertainty due to systematic bias in gamma dose estimates, denoted D_γ in NCRP 126 with error factor $f(D_\gamma)$ distributed as triangular(1.0, 1.1, 1.4).

4) Uncertainty due to systematic bias in neutron dose estimates in Hiroshima, denoted D_n in NCRP 126 with error factor $f(D_n)$ distributed as triangular(1.0, 1.1, 1.3).

The overall error factors for random and systematic errors in dosimetry are

$$F_L(D) = (1+F_L(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for solid tumors and

$$F_Q(D) = (1+F_Q(R_E))/(F(N_R)\times F(D_\gamma)\times F(D_n))$$

for leukemia. The uncertainty distributions for $F_L(D)$ and $F_Q(D)$, expressed in percent, correspond reasonably well to normal distributions: N(83.2, 8.36) and N(80.7, 8.05), respectively.

F. Dependence of risk on dose and dose rate for low-LET radiation

Radiations of different quality differ with respect to the shape of the dose-response function for cancer risk. Risk per unit dose of radiations of high linear energy transfer (LET), such as neutrons, alpha particles, or heavy ions, tend to be the same (or greater) at low compared to high doses, whereas for low-LET radiations, such as gamma rays, electrons, x rays, or beta particles, risk per unit dose is thought to be lower at low dose levels. Evidence for a lower risk per unit dose or unit equivalent dose (henceforth to be referred to simply as "dose") of low-LET radiation at low (compared to high) dose levels comes mainly from experimental radiobiology, much of it involving outcomes other than carcinogenesis (NCRP, 1980). Inferences about the shape of the dose-response relationship based on epidemiological studies of cancer, on the other hand, tend to be determined by data in the middle and high dose ranges, i.e., 0.1-1.0 Gy and 1.0 Gy and higher. For solid cancers, generally, there is little persuasive epidemiological evidence of nonlinearity of dose response, whereas for leukemia there is good evidence of positive curvature. The linear-quadratic dose-response model for leukemia used here corresponds to a risk at 0.01 Gy (1 cGy) that is only 0.5% as high as the risk at 1 Gy, or half as high per unit dose.

Linear-model risk coefficients may be reduced by a dose and dose-rate effectiveness factor (DDREF) for estimating risks at low doses and low dose rates. The International Commission on Radiological Protection (ICRP, 1991) recommended a DDREF of 2 for purposes of radiation protection, a value roughly consistent with the default linear-quadratic dose-response model used here for leukemia. The ICRP recommendation is also accepted by the NCRP (1993). In their most recent discussion of the application of DDREF, the United Nations Subcommittee on Effects

of Atomic Radiation (UNSCEAR, 1993) recommended that the chosen DDREF be applied to chronic exposures (dose rates less than 6 mGy per hour averaged over the first few hours) and to acute (high dose rate) exposures at total doses less than 0.2 Gy, a recommendation that was subsequently adopted by the EPA (1999). However, such an abrupt transition seems unrealistic in view of observed linearity of dose response for cancer incidence and mortality among acutely exposed A-bomb survivors, down to and including values below 0.2 Gy (Thompson et al., 1994, Pierce et al., 1996). Also, continuous uncertainty distributions for DDREF have been used by NCRP (1997), EPA (1999), and in a report prepared for the Colorado Department of Public Health and Environment (Grogan et al, 2000) for calculations of lifetime risk of all cancer types combined (Figure IV.F.1). The Grogan et al uncertainty distribution differs from the NCRP distribution mainly in allowing a small probability that risk per unit dose might increase at very low doses. Thus, the NCRP and EPA distributions allowed for the possibility of DDREF values between 1 and 5, while the Grogan et al distribution included values as low at 0.2.

In the present report, ERR is estimated as a function of radiation dose, and modified according to exposure rate (acute or chronic) by application of an uncertain DDREF. The DDREF is applied to all chronic exposures whereas, for acute exposure, the DDREF is phased in as dose is decreased, beginning at an uncertain reference dose less than 0.2 Sv and decreasing smoothly to the value appropriate for chronic exposure. Fractionated acute exposures separated by 5 hours or more are treated as separate exposures; thus, the DDREF is applied to each fraction and their estimated effects on risk are added together. The working group has chosen to derive its own subjective uncertainty distribution for DDREF ($DDREF_{chronic}$) (Figure IV.F.2, left-hand panel), mainly because the analysis of low-dose LSS cancer mortality data (Pierce et al, 1996) is strongly consistent with linearity and suggests, however weakly, the possibility of supra linearity of dose response below 0.5 Sv. A discrete, rather than continuous, distribution was used (emphasizing the subjective nature of the exercise), with nonzero probabilities on DDREF = 0.5, 0.7, 1, 1.5, 2, 3, and 5. For cancers of the female breast and the thyroid gland, a discrete distribution was selected with greater probability at DDREF = 1 (Figure IV.F.2, right-hand panel).

For an *acute* exposure, the DDREF ($DDREF_{acute}$) is modeled as a random quantity that approaches $DDREF_{chronic}$ as dose decreases to zero. Between zero and an uncertain reference dose, D_L (between 0.03 and 0.2 Gy), $DDREF_{acute}$ increases smoothly from $DDREF_{chronic}$ at zero dose to 1 at D_L and above, according to a logistic function of dose (Figure IV.F.3). The uncertainty in the reference dose D_L is expressed as a log-uniform distribution (Figure IV.F.4).

G. Transfer of ERR from the Japanese to the U.S. population

A major concern in using data from Japanese A-bomb survivors to estimate risks for specific cancers in a U.S. population is that baseline risks differ between the two populations and the dependence of radiation risks on baseline risks is not known with certainty. For example, baseline

cancer rates for breast, lung and colon cancer are smaller in Japan than in the United States, while rates for stomach and liver cancer are much higher in Japan. Estimation of risk for a U.S. population based on the dose response coefficients derived from A-bomb survivor data is commonly referred to as the "transfer" or "transportation" problem. A more detailed discussion of the transfer problem appears in NCRP Report 126 (NCRP, 1997).

Two simple solutions are the so-called "multiplicative" and "additive" transfer models, in which estimates of excess relative risk (the ratio between excess and baseline risk) and absolute risk (the difference between the estimated cancer rates with and without exposure), respectively, are applied to the second population (in this case, the U.S. population). The multiplicative transfer model is biologically plausible to the extent that ionizing radiation exposure can be assumed to act as an "initiator" of a process whose likelihood of resulting in cancer depends upon the action of "promoting" agents, if these "promoting" agents are responsible for the difference in baseline rates between the two populations, or, alternatively, if radiation were to act as a promoter of the carcinogenic effects of other agents that are differentially effective in the two populations. In this view, the excess risk from radiation exposure would be greater in a normally high-risk population than in a normally low-risk population. The additive transfer model is plausible to the extent that radiation can be assumed to act mainly as an initiator and the difference between population baseline rates can be assumed to be due to the differential effects in the two populations of other "initiator" carcinogens that act similarly to radiation. In this view, the additional cancer risk burden of radiation exposure would be independent of the population baseline rate.

Several approaches have been used for transferring risk estimates based on the Japanese A-bomb survivor data to other populations. The multiplicative transfer model was used by UNSCEAR (1988) for the world population and in the BEIR V report (NAS, 1990) for the U.S. population. The additive transfer model was used in the BEIR III report (NAS, 1980) and the 1985 NIH report (NIH, 1985). The two transfer models can lead to very different estimates of radiation-related risk for certain cancers for which baseline risks differ greatly between Japan and the U.S. (Land, 1990). Each model receives some support from site-specific comparisons, but there are few sites for which meaningful analytic comparisons can be made. If population differences in cancer rates may be due to both initiating and promoting agents, it is likely that both additive and multiplicative model interactions with radiation may take place, and that some kind of mixture model may be appropriate. For example, the ICRP (1991) used the arithmetic mean of the ERR values obtained by the two transfer models for all solid cancer types combined (Land and Sinclair, 1991), and the Environmental Protection Agency (Puskin and Nelson, 1995) used the geometric mean (except for liver cancer associated with exposure to the radioactive contrast medium thorotrast and bone cancer from exposure to injected ^{224}Ra, for which an additive transfer model was chosen). More recent reports have used uncertain (i.e., randomized) linear or geometric combinations, weighted in various ways, of the additive and multiplicative transfer models for the

estimation of total risk of cancer mortality (EPA, 1999).

Mortality rates for all types of cancer combined vary relatively little by nation, compared to site-specific variation. The initial ERR_{1Sv} value for mortality from all cancers combined used in NCRP Report 126 (NCRP, 1997) was the rounded average of multiplicative and additive transfer model estimates from the LSS mortality data for five different national populations (ICRP, 1991, Land and Sinclair, 1991). Thus, the problem for that report was not how to estimate ERR_{1Sv} for a US population, but to determine the uncertainty associated with estimating ERR_{1Sv} in a particular way. Their solution was an uncertainty factor $f(T)$, distributed as LN(1, 1.3).

For the present report, the problem is how to estimate site-specific and age-specific values of ERR_{1Sv} for the US population in the presence of possibly large differences in baseline rates and the absence of useful information about which model might be correct. Our approach is to use a random linear combination between the additive and multiplicative models,

$$(ERR_{1Sv})_{US} = y \times (ERR_{1Sv})_{mult} + (1-y) \times (ERR_{1Sv})_{add},$$

where the random variable y varies between -0.1 and 1.1. Here, $(ERR_{1\,Sv})_{mult}$ is the site-, sex-, and age-specific excess relative risk at 1 Sv obtained from statistical analysis of the Japanese A-Bomb survivor data and adjusted for random and systematic errors in dose to individual A-bomb survivors (see IV.D above). $(ERR_{1\,Sv})_{add}$ is the same value, adjusted for the corresponding ratio between baseline rates in the two countries:

$$\left(ERR_{1Sv}\right)_{add} = \left(ERR_{1Sv}\right)_{mult} \cdot \left(\frac{B_{Japan}}{B_{US}}\right)$$

Here, B_{Japan} and B_{US} are the sex- and site-specific, age-adjusted background cancer incidence rates in Japan (a surrogate for the A-Bomb survivor cohort) and the US population, respectively, both age-standardized to the world population age distribution (Parkin, 1997).

The coefficient y of the linear combination can be used to favor one model or the other according to the weight of evidence. For instance, y=0 corresponds to the *additive* model, $y = 1$ to the multiplicative model, and $y = ½$ to the arithmetic average of the two. A Monte Carlo simulation is used to express uncertainty about y, with y values sampled according to the following probability density distribution:

$$f(y) = 0.9091 \times \begin{cases} (y+0.1) & -0.1 < y < 0 \\ 1 & 0 \le y \le 1 \\ (1.1-y) & 1.0 < y < 1.1 \end{cases}$$

The constant probability density shown above for y values between 0 and 1 reflects a complete lack of knowledge about the appropriateness of particular weighted averages of the additive and multiplicative transfer models, and the assignment of a small probability weight (9%) to values less than zero and larger than one allows for the (subjectively unlikely) possibility that radiation-related cancer risk might be negatively correlated with population baseline risk. For breast and stomach cancer, more information is available and, thus, the "uninformed" trapezoidal density given above and in Figure V.G.1 may be modified by redistributing some of the weight to the additive transfer model in the case of breast cancer (Land et al, 1980, Little and Boice, 1999, Mattson, 1999) or the multiplicative model for stomach cancer (Griem et al, 1994, Carr et al, 2002). Thus, for breast cancer, a probability weight of 50% was assigned to the *additive* transfer model ($y = 0$), and 50% was assigned to the trapezoidal probability density distribution. For stomach cancer, a probability weight of 33% was assigned to the *multiplicative* model ($y = 1$), and 66% to the trapezoidal distribution, while for thyroid cancer the weighting was 50% on the multiplicative model and 50% on the trapezoidal distribution, reflecting the international basis of the Ron study (1995). The cumulative distribution functions for these distributions are compared with that for the "uninformed" distribution in Figure IV.G.2.

H. Radiation effectiveness factors for different radiation types

People can be exposed to many different types of ionizing radiation including photons, electrons, alpha particles, and neutrons, and the energies of each radiation type can vary widely. Many studies of the effects of ionizing radiation on a wide variety of biological systems, ranging from simple cells to complex whole organisms, have shown that different types of radiation often differ substantially in their biological effectiveness. That is, the probability that a particular biological response is induced by radiation depends on the radiation type and sometimes its energy, as well as the dose. In estimating cancer risks and probability of causation (assigned share) for an individual who received known exposures to particular radiation types, it therefore is essential that differences in the biological effectiveness of the different radiations be taken into account.

Differences in biological effectiveness of different radiation types have long been taken into account in radiation protection. The quantity currently used in radiation protection to describe the biological effectiveness of different radiation types is the radiation weighting factor. This factor is used to modify the dose in an organ or tissue of humans from a given radiation type (the total energy imparted in the organ or tissue divided by its mass), given in Gy, to yield an estimate of equivalent dose, given in Sv. The risk of cancer (or other stochastic radiation effect) in an irradiated organ or tissue is assumed to be proportional to the equivalent dose, independent of radiation type.

The assigned point values of radiation weighting factors used in radiation protection are based on data on the relative biological effectiveness (RBE) of radiations obtained from radiobiological studies of a variety of responses in different biological systems, as well as judgments about the

applicability of estimated RBEs to induction of cancers in humans and theoretical considerations of the relationship between biological effectiveness and the density of ionization produced by different radiations in tissue. The radiation weighting factors currently used in radiation protection include: 1 for photons and electrons of any energy; 20 for alpha particles; and 20 for neutrons of energy 0.1-2 MeV including fission neutrons, 10 for neutrons of energy 10-100 keV or 2-20 MeV, and 5 for neutrons of energy less than 10 keV or greater than 20 MeV. Thus, photons and electrons have a biological effectiveness of 1, by definition, and the radiation weighting factors for the other radiation types represent judgments about their biological effectiveness in humans relative to photons and electrons.

For the purpose of estimating cancer risks and assigned shares in identifiable individuals who received known (estimated) radiation exposures, the term "radiation effectiveness factor," denoted by REF, has been developed to describe the biological effectiveness of different radiation types (Kocher et al., 2002). There are two reasons why a new term, other than "RBE" or "radiation weighting factor," is used. First, "RBE" is not appropriate because this quantity strictly applies only to results obtained from specific radiobiological studies and, thus, should not be used to describe an extrapolation of such results to a different biological endpoint, biological system, or condition of exposure. Second, as discussed above, the radiation weighting factor is a prescribed point quantity, without uncertainty, which is used in radiation protection to calculate equivalent doses, but it is not intended to be used to estimate cancer risks and assigned shares in identifiable individuals who received known exposures. Furthermore, cancer risks and assigned shares are estimated based on estimates of dose without the need to estimate equivalent doses, and it is essential that uncertainties in the biological effectiveness of different radiation types relative to a defined reference radiation be taken into account.

The radiation effectiveness factor for a particular radiation type is used in estimating cancer risks and assigned shares from actual exposures in accordance with one of the following equations:

Solid tumors –

$$\mathfrak{R} = \mathrm{REF_L} \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma} \times D \,, \qquad \text{(IV.H.1)}$$

$$\mathfrak{R} = \mathrm{REF_H} \times R_{\gamma,\mathrm{H}} \times D \,, \qquad \text{(IV.H.2)}$$

Leukemias –

$$\mathfrak{R} = a \times \mathrm{REF_L} \times D \,, \qquad \text{(IV.H.3)}$$

$$\mathfrak{R} = a(\mathrm{REF_L} \times D) + b(\mathrm{REF_L} \times D)^2 \,. \qquad \text{(IV.H.4)}$$

In these equations –

- $\mathfrak{R}$ is the risk of a particular cancer (i.e., the excess relative risk, ERR) due to

exposure to a particular radiation type;

- REF is the radiation effectiveness factor for the radiation type and cancer type of concern;
- the subscripts "L" and "H" denote low doses and dose rates and high doses and dose rates, respectively;
- $R_{\gamma,H}$ is the risk coefficient (ERR per Gy) at high doses and high dose rates of the reference high-energy gamma (γ) radiation with a defined biological effectiveness of 1, assuming linearity in the dose-response relationships for all solid tumors;
- DDREF is the dose and dose-rate effectiveness factor, which takes into account that the ERR per Gy for solid tumors at low doses and dose rates of photons (and electrons) may be less than the values of $R_{\gamma,H}$ obtained from studies of exposed populations;
- a and b are the coefficients of the linear and quadratic terms in a linear-quadratic dose-response relationship which is assumed for leukemias under conditions of acute exposure to high-energy gamma rays; and
- D is the estimated dose from the radiation type of concern.

For most solid tumors, the risk coefficients at high doses and dose rates of high-energy gamma rays, $R_{\gamma,H}$, are obtained from studies of the Japanese atomic-bomb survivors. The coefficients a and b in the linear-quadratic dose-response relationship for leukemias under conditions of acute exposure to high-energy gamma rays also are obtained from studies of the atomic-bomb survivors. The data on leukemias indicate that the two coefficients are approximately equal numerically, and this assumption is used in this work. In the radiation effectiveness factor (REF) for the radiation type of concern, the subscripts L and H denote that this factor is estimated based on data on RBE at low doses and dose rates or at high doses and dose rates of the reference radiation, respectively.

The equation selected depends on the particular radiation type and cancer of concern. As discussed by Kocher et al. (2002), eq. (1) for solid tumors is used in cases of exposure to photons, electrons, and alpha particles, eq. (2) for solid tumors is used in cases of exposure to neutrons, eq. (3) for leukemias is used in cases of exposure to alpha particles and neutrons and in cases of chronic exposure to photons and electrons, and eq. (4) for leukemias is used in cases of acute exposure to photons and electrons. Not shown in eqs. (1)-(3) is a factor representing an inverse dose-rate effect, which is applied to all exposures to alpha particles and to chronic exposures to neutrons. This factor, which is a multiplier on the right-hand side of these equations, takes into account that the biological effectiveness of high-LET radiations may be higher under conditions of chronic exposure than under conditions of acute exposure. The use of eqs. (1)-(4) is discussed

further later in this section.

As noted previously, uncertainties in radiation effectiveness factors for different radiation types are taken into account in estimating cancer risks and assigned shares. These uncertainties are described by means of subjective probability (uncertainty) distributions. The assumed probability distributions are intended to represent judgments about the current state of knowledge of the effectiveness of the different radiation types, relative to high-energy gamma rays, in inducing cancers in humans; they are not intended to represent statistical distributions of results that would be obtained if radiobiological studies of the effectiveness of the different radiations in inducing cancers in humans were performed. The factors representing an inverse dose-rate effect for alpha particles or neutrons under conditions of chronic exposure also are described by subjective probability distributions.

The probability distributions of the radiation effectiveness factors used in this report were developed by Kocher et al. (2002) of *SENES* Oak Ridge under contract with the National Institute of Occupational Safety and Health (NIOSH), and have taken into account peer reviews of the work by NIOSH consultants. The assumed probability distributions of the radiation effectiveness factors for photons and electrons are summarized in Table IV.H.1, the distributions for alpha particles are summarized in Table IV.H.2, and the distributions for neutrons are summarized in Table IV.H.3. For photons and electrons, the probability distributions of the radiation effectiveness factors are applied to all cancers, whereas separate probability distributions are developed for leukemias (including lymphomas and lymphocytic cancers) in cases of exposure to alpha particles and neutrons. The probability distributions of the correction for an inverse dose-rate effect are included in the tables for alpha particles and neutrons.

The procedure for using eqs. (1)-(4) in estimating cancer risks and assigned shares is as follows. It is assumed that the exposure history of an individual is given in terms of the equivalent dose, in Sv, to the organ or tissue in which a cancer has occurred—i.e., the dose in that organ or tissue modified by a standard radiation weighting factor, denoted by w_R (formerly called the average quality factor, $\overline{Q}$)—and that the equivalent dose is given for each radiation type (photons, electrons, alpha particles, and neutrons) separately. From the given equivalent dose for a particular radiation type in an organ or tissue (T), denoted by H_T, the dose (D) in that organ or tissue, in Gy, is calculated as $D_T = H_T/w_R$. The dose for each radiation type is the quantity that is input to the calculation of cancer risk and assigned share, and each of these doses is modified by the relevant radiation effectiveness factor in accordance with the appropriate equation.

The treatment of the biological effectiveness of the different radiation types of concern, as represented by the probability distributions of the radiation effectiveness factors summarized in Tables IV.H.1-IV.H.3, differs from the 1985 NIH report in two respects. First, with the exceptions of lung cancer among uranium miners exposed to inhaled radon and its short-lived decay products, with exposure expressed in working level months (WLM), and bone cancer

among patients injected with the short-lived alpha emitter ^{224}Ra, the 1985 report considered only radiations for which the biological effectiveness was assumed to be unity (i.e., photons). It was recognized that, at low doses and dose rates, high-energy gamma rays might be less damaging than lower-energy X rays, but the NIH working group did not have sufficient information to make such a distinction. In the present work, the biological effectiveness of all radiation types (photons, electrons, alpha particles, and neutrons) is taken into account for all cancers, with the exception that radon and lung cancer continues to be treated separately based on estimates of exposure in WLM. In particular, a distinction is made between the effectiveness of high-energy gamma rays and lower-energy X rays, as well as low-energy electrons. The second important difference is that uncertainties in the biological effectiveness of all radiation types relative to high-energy gamma rays are now taken into account. Since the 1985 NIH report focused on radiations that were assumed to be equally effective at any energies, there was no need at that time to consider uncertainties in biological effectiveness.

I. Modification by epidemiological risk factors

Site-specific studies of radiation dose and cancer risk, in LSS sample and in other exposed populations continually followed up over time, generally proceed in a series of steps beginning with the evaluation of evidence that a dose-related excess risk actually exists. Usually, the first modifiers of dose response to be considered are gender, age at exposure, age at observation (attained age), and time following exposure, since information about them is usually obtained at the same time as information on radiation exposure and disease occurrence. Modification of dose response by other factors is a more difficult problem, because it usually requires special data-gathering efforts, such as with an embedded case-control study. Informative studies of interaction between radiation dose and epidemiological risk factors have been carried out for reproductive history in the case of breast cancer and for smoking history in the case of lung cancer.

1. General formulation. If radiation dose D and factor *f* are multiplicative in effect, then the excess relative risk associated with exposure D is independent of *f*, i.e., $ERR_{D|f} = ERR_D$. If D and *f* are additive in effect, then the conditional ERR associated with D given exposure *f* is

$$ERR_{D|f} = ERR_D/(1+ERR_f).$$

2. Breast cancer: interaction of radiation and age at first full-term pregnancy. Reproductive history is known to be an important breast cancer risk factor. In particular, early age at first full-term pregnancy has been shown, in virtually every population that has been studied, to be protective. A case-control interview study of female A-bomb survivors examined the interaction of this risk factor with radiation dose (Land et al, 1994), and found that an additive interaction model was rejected, whereas a multiplicative interaction model was consistent with the data. A general risk model,

$$R_{mix}(D,X;\beta,\theta) = (1 + \alpha_E D)(1 + \beta X/\{1 + \alpha_E D\}^{\theta}),$$

was used to distinguish between the multiplicative model (corresponding to $\theta=0$),

$$R_{mult}(D,X;\beta) = (1 + \alpha_E D)(1 + \beta X),$$

and the additive model (corresponding to $\theta=1$),

$$R_{add}(D,X;\beta) = 1 + \alpha_E D + \beta X.$$

Here, D is radiation dose, X is age at first full-term pregnancy, α_E is a parametric function describing radiation dose response as a function of age at exposure E, and β is an unknown parameter corresponding to X. The maximum likelihood estimate of the parameter θ was negative (-0.25) (Land, 1994) and the likelihood distribution placed less than 10% probability on values greater than zero in calculations performed for the present report. Thus, it appears that very little additional uncertainty would be contributed by allowing for deviations from the multiplicative interaction model, for which no adjustment of ERR_{1Sv} is required for age at first full-term pregnancy. This report therefore makes no uncertainty adjustment for this factor.

3. Lung cancer: interaction of radiation dose with smoking history. Interaction analyses of A-bomb survivors (Blot et al, 1983) and uranium miners (NAS, 1988) failed to discriminate between additive and multiplicative interaction models, although the BEIR IV committee concluded that the data were more consistent with a multiplicative interaction (NAS, 1988). More recently, Lubin and Steindorf (1995) modeled joint relative risks for smoking history (ever vs. never) and exposure to inhaled radon decay products among 6 cohorts of U.S. uranium miners for which such information was available. They concluded that, at that level of smoking history detail, the best-fitting interaction model was intermediate between the additive and multiplicative interaction models. The BEIR VI committee (NAS, 1999) applied the Lubin-Steindorf approach using more recent data, and concluded that both the multiplicative and (especially) the additive interaction models were statistically inconsistent with the data.

In the 1985 NIH report, it was assumed that the interaction of smoking and exposure to low-LET radiation was additive with appropriate assigned shares obtained by multiplying the ERRs by the factors indicated in columns 2 and 3 of Table IV.I.1. These factors were calculated as described on pp. 48-51 of the 1985 report and based on lung cancer relative risks by smoking category given by Rogot and Murray (1980) and the distribution of the U.S. population by smoking status in 1964-65 as published by the National Center for Health Statistics (1967). These factors can be updated by using 1993 information on the smoking status distribution provided by the Centers for Disease Control (1995). This distribution differs substantially from that used in the 1985 report as shown in Table IV.I.2. Because the CDC report did not provide data on amount smoked, it was assumed that among current smokers the distribution by amount smoked was the same as that used in the 1985 report (p.50). It was also assumed that the relative risks by smoking category remained appropriate. The revised factors for additive transportation are given in the last two columns of Table IV.I.1. For the purposes of this report, the ERR_{1Sv} for lung cancer is multiplied

by a factor W_S taken to be $x + (1- x)W_S^*$, where S indexes smoking categories, the W_S^* are the factors given in columns 3 and 4 of Table IV.I.1, and x is assumed to follow a triangular distribution (0, 1, 1.1). This uncertainty distribution allows the ERR_{1Sv} for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$), with a probability of about .10 for a super-multiplicative interaction ($x > 1$). The median of this distribution is .74, and at this value, $W_S = 1.97$ for male never-smokers, $W_S = 0.87$ for male ever-smokers, $W_S = 1.75$ for female never-smokers, and $W_S = 0.85$ for female ever-smokers. Thus, at the median value, the ERR_{1Sv} for never smokers is a little more than twice that for ever-smokers. A ratio of two was used by the BEIR VI committee, and was obtained from analyses of uranium miner data (NAS, 1999, pg. 154).

4. Basal cell skin carcinoma: interaction between ionizing and ultraviolet radiation. Ron et al (1998) found significantly different ($p<.02$) ERR_{1Sv} values for basal cell skin carcinoma occurring on the face and hands (0.4, 90% CI -0.1-2.1) and on the rest of the body (4.7, 1.2-1.3), suggesting a sub-multiplicative, or possibly even additive, interaction between UV and ionizing radiation. This finding suggests that ERR_{1Sv} in lighter-skinned, and therefore more UV-sensitive, populations could be less than that observed in the LSS population. On the other hand, Shore et al (2002) reported 124 BCSC cases among 1699 white patients treated by X-ray during childhood for scalp ringworm, cf. 21 among 1035 white nonexposed patients. Among African-Americans, however, only 3 BCSC cases were seen among 525 exposed patients vs 0 among 345 non-exposed patients. This result, unlike that of Ron et al, is inconsistent with additive interaction between ionizing radiation and protection from ultraviolet radiation by skin pigmentation or clothing, as risk factors for BCSC. Judging that we do not now have a good basis for evaluating this interaction, the Working Group has chosen to use the "complete ignorance" uncertainty model discussed in section IV.I above for transfer of the A-bomb survivor-based ERR_{1Sv} estimates for BCSC to the U. S. population and to subpopulations with different baseline BCSC rates.

J. Susceptible subgroups.

Genetic susceptibility to radiation carcinogenesis is known to occur in patients with xeroderma pigmentosum or hereditary retinoblastoma, and the possibility of other such associations is of great interest for theories of carcinogenesis. However, most known genetic syndromes predisposing to cancer are rare, and interactions with radiation dose have not been quantified (ICRP, 1998). Such interactions therefore have not been explored in the present report.

K. Additional sources of uncertainty

As mentioned above (section IV.A), AS is not intended to represent the probability that a particular individual's cancer was caused by his or her radiation exposure, but rather, the fraction of cases of a particular kind of cancer, diagnosed at a particular age among a large group of U.S. residents with a similar exposure history, that would not have occurred in the absence of that exposure. Possible modifying effects of age at exposure, gender, age at diagnosis, and time following exposure, plus (for certain sites) smoking history and reproductive history have been

studied and that information has been incorporated into the model. The working group has also introduced crude uncertainty factors for transfer of risk coefficients between populations with different baseline risks.

It is likely that there are other sources of bias and uncertainty influencing radiation-related risk and AS, about which we have no useful information and, thus, no solid grounds for taking action. However, there may be instances where a case can be made for additional uncertainty. Following the recommendation of the NRC review committee (NRC, 2000) that any additional uncertainty adjustment be documented and justified by an authoritative review panel, we have provided the option for such an adjustment in the expectation that it would be used very rarely, if at all.

V. Features of the Approach

A. This is an interim update.

As noted in III A and B, in the last 15 years additional epidemiologic data have become available, and these data have considerable potential for modifying and refining the AS tables now in use. Also, several efforts have been made to summarize data that were not available at the time the NIH report was published, and to develop risk estimates based on these data. However, these efforts have not evaluated data from studies published in very recent years, including particularly the latest updates of the Japanese A-bomb survivor incidence and mortality data. For example, the most recent BEIR assessment was published in 1990 and the most recent ICRP assessment was published in 1991. Thus, much of the available new data has not yet been evaluated by expert committees charged with developing and recommending risk estimates. In addition, new data, including updated follow-up for cancer incidence in the A-bomb survivors, are currently being evaluated at RERF.

In part because of this situation, the BEIR VII - Phase 1 Committee has recommended that a reassessment of the health effects of exposure to low levels of ionizing radiation be conducted, and the BEIR VII - Phase 2 has been formed to undertake this task. It is anticipated that the present report will be revised after the BEIR VII committee recommendations become available, expected in two or three years. Thus, the AS algorithms described here must be regarded as an interim update rather than one based on risk models endorsed by an official national or international committee; therefore, it might differ appreciably from future tables based on the BEIR VII - Phase 2 report. The current update nevertheless provides AS values that are based on more up-to-date data and models than previously, and also makes notable improvements in the treatment of uncertainties.

B. Similarities to the 1985 report

Because this update must be regarded as interim, the time frame and scope for carrying out data analyses and model development were limited. For this reason, we did not begin from scratch to develop new models, but instead used the models used for the 1985 AS tables as a starting point, amending them as needed to reflect the most important changes in risk coefficients and risk modeling approaches. Specifically, the following features of the 1985 tables were retained:

1. Assigned share estimates based primarily on A-bomb survivor data. The AS values in the 1985 report were based primarily on the A-bomb survivor data, although in some cases other data were also used. The AS values in the current report are based almost entirely on A-bomb survivor data and, with the exception of thyroid cancer, did not directly make use of data from studies of persons exposed for medical reasons, or from studies of workers and others exposed at low doses and dose rates. Estimates based on data from low dose studies would be far too imprecise to meet the needs of the AS tables, where estimates for specific cancer, ages at exposure and gender are required. It is noted, however, that considerable uncertainty has been allowed for extrapolation from high doses and dose rates.

2. Cancer sites evaluated include most of those in the 1985 report. Our choice of cancer sites

includes all but one of those in the previous report. The LSS tumor registry data include only 15 bone cancer cases, too few for inclusion as a separate site. Bone cancer associated with injection of ^{224}Ra, which was included in the 1985 report, was not included in the present report because, although an estimate of radiation-related risk is well-supported by epidemiological data from the Spiess series (Nekolla, 2000), compensation claims associated with injection of ^{224}Ra are highly unlikely to be presented to either the DVA or DOL. Moreover, the remarkable distribution of radiation-related risk over time following injection does not appear to be characteristic of exposure to either gamma ray or other isotopes of radium, and the risk estimates would be difficult to extrapolate to those exposures. Several new cancer categories have been added.

3. Treatment of latent period. The time required for radiation exposure to be reflected in terms of excess cancer risk in an exposed population is very difficult to estimate. In the present report, excess relative risk, which itself may depend on attained age and, in the case of leukemia, on time following exposure, is multiplied by an S-shaped function of time after exposure, that increases from zero immediately after exposure to one after a transition period. The rapidity of the increase depends upon cancer site, with an early increase, becoming appreciable 2 years after exposure and reaching full value after 6 years for leukemia, a somewhat slower increase for thyroid cancer beginning after 3 years and ending after 8 years, and, for all other solid tumors, an increase beginning after 3 years and ending after 14 years. This is only slightly different from the approach of the 1985 report.

C. Important changes

1. Estimates were obtained for all cancer sites for which the calculations could be performed, not just those established as "radiation-related." A working assumption was that radiation exposure might be a causal factor for any site or type of cancer, at some exposure level and under some conditions. This assumption obviates the question of whether or not a particular kind of cancer could be caused by radiation; rather, the most pertinent problem is what values of AS are consistent with current scientific information in a particular instance of cancer following a particular exposure. The working group therefore has provided for the calculation of uncertainty distributions for AS, for all cancer types for which there were relevant data available from the sources on which the present report is based.

2. Assigned share estimates were based on incidence instead of mortality data. Although the 1985 NIH report used incidence data from site-specific studies of leukemia and cancers of the thyroid gland, female breast, and salivary gland, it relied mainly on data from the LSS mortality survey. By contrast, the present report bases its estimates and models on data from the LSS Tumor Registry and, in the case of thyroid cancer, from a pooled analysis of data from several studies. The RERF Tumor Registry is now a highly reliable source of cancer incidence information with good coverage of that part (80%) of the surviving LSS sample resident in the environs of Hiroshima and Nagasaki (Mabuchi, 1994); this coverage goes far toward matching the main advantage of the LSS death certificate data, viz., completeness of ascertainment for a general population of both genders and all ages, acutely and simultaneously exposed to a range of whole-body radiation doses and followed uniformly over time. Follow-up for the mortality series and for incident diseases covered by the Leukemia Registry began on October 1, 1950, the entry date

for members of the LSS cohort; for the LSS Tumor Registry, follow-up began on January 1, 1958. The later beginning of the tumor registry is a serious problem only for cancers of short latency, most of which are covered by the Leukemia Registry or by site-specific studies that involved special case-ascertainment efforts for the period 1950-1957, and for estimation of excess risk among persons who were over 50 or 60 years of age when exposed. Comprehensive statistical analyses of site-specific cancer incidence through 1987 were presented for solid cancers and leukemia (Thompson, 1994, Preston, 1994) and, especially important for present purposes, the original data sets were made available by RERF on disk or downloadable from the RERF web site.

3. Assigned share estimates are based on analyses conducted for this specific purpose instead of published risk estimates. For the 1985 report, assigned shares were estimated from tabulated published estimates, primarily from the BEIR III report. The availability of grouped numerator and denominator data from LSS Tumor Registry for 1958-1987, plus similar data from a site-specific incidence study of skin cancer and a pooled study of thyroid cancer in several irradiated populations, allowed the present working group to model site-specific risks directly. This permitted the working group to determine independently the dependence of dose-specific excess relative risk on important modifying factors, and to choose models of suitable complexity.

4. Modeling of the excess relative risk (ERR) instead of the excess absolute risk (EAR). The ERR was modeled directly rather than converted from tabulated estimates of EAR, as was done in the 1985 report. Note that assigned share (AS) is a simple, monotonic function of the ERR, AS = ERR /(1+ERR).

5. More attention to attained age. For all cancer types except leukemia and bone cancer, the 1985 report models were based on the assumption that, after a minimal latent period, the excess relative risk per Sv (ERR/Sv) remained constant over time since exposure and therefore did not depend additionally upon attained age. New information from analyses of A-bomb survivor information suggests that this may not be the case generally. Modeling for the present report allows for the possibility that ERR/Sv may depend upon attained age as well as age at exposure..

6. Different default assumptions for dependence of ERR/Sv on exposure age and attained age. In the 1985 report and in the 1990 draft report presented to the NRC review committee, site-specific estimates of ERR/Sv were fitted separately by site, and were assumed not to depend upon sex, age at exposure, or attained age unless there was site-specific statistical evidence to the contrary. The NRC review subcommittee recommended that consideration be given to conducting joint analyses of several cancer types (see Pierce and Preston, 1993), testing whether various parameters were comparable among cancer types, and then using common estimates of selected parameters in developing site-specific AS values. This approach has the potential advantage of greater statistical precision in the estimated AS values, but the disadvantage of difficult-to-quantify uncertainty in whether the chosen models are appropriate. Our approach was to estimate parameters for modification of ERR/Sv by exposure age and attained age for all solid cancers combined and to use these as default values for site-specific estimates. Thus, values fitted from site-specific data alone were used only if they differed significantly from the default values. Type-specific leukemia estimates were based on type-specific data only, and included nonzero

modifying parameters by time, exposure age, or attained age only if required.

7. Radiation dose response and adjustment for low dose-rate exposure Because estimates obtained directly from epidemiological data on populations exposed only at low doses are very imprecise, it is necessary to extrapolate from risks that have been estimated from persons exposed at higher doses (and dose rates) than those of direct interest. The estimates used in this report are based on Japanese atomic bomb survivor data, and estimates based on these data tend to be driven by the cancer experience of persons exposed to doses that exceed 1 Gy. This is much larger than doses for which AS values are usually desired, which are almost always less than 0.1 Gy and often much smaller.

Although most epidemiological data for solid cancers are compatible with a linear dose-response function in which risk is proportional to dose, curvilinear forms cannot be excluded. On the other hand, dose-response analyses of leukemia risk have consistently shown evidence of upward curvature consistent with a quadratic function of dose having a substantial linear component ("linear-quadratic" or "L-Q" for short).

a. Method used in the 1985 NIH report The 1980 BEIR III committee chose as their "preferred" dose response model an L-Q model in which risk was proportional to $D + D^2/1.16$, where D is organ-specific dose in Gy, and the 1985 NIH tables committee adopted that form for their report. Thus, with two exceptions (breast and thyroid cancer, for which linearity was assumed), the estimated excess risk per unit dose was a little more than half as high at 0.1 Gy as at 1 Gy. Another consequence was that the risk per unit dose of the sum of several exposures, each less than 0.1 Gy and separated in time, or a chronic exposure (treated much the same as the sum of many very small exposures) was estimated to be about half as high as that for a single, acute exposure of about 1.2 Gy.

b. Method used in the present report The approach used for the present report was to treat leukemia risk as proportional to $D + D^2$, since estimates of the D^2 coefficient are generally inexact but in the neighborhood of unity and significantly greater than zero. For all other cancers, the risk was assumed to be linear (proportional to D) for curve-fitting purposes but with a dose-and-dose-rate-effectiveness factor (DDREF) applied to reduce estimated risk at low doses and dose rates. The DDREF approach was chosen because it is consistent with recommendations by the International Commission on Radiation Protection (ICRP, 1991) and because instances of a linear dose response have been observed above a certain level in combination with a DDREF of 2 or more at lower levels, in experimental studies of radiation carcinogenesis using fractionated exposures (R. Ullrich, personal communication).

8. Transfer of estimates between populations. An important source of uncertainty is the applicability of risk estimates derived from Japanese A-bomb survivor data to a contemporary U.S. population, especially for cancer types where baseline risks for the two countries differ markedly. On the basis of comparisons of leukemia and breast cancer risk in different populations (BEIR III, Land et al, 1980), transfer between populations in the 1985 NIH report was based on the assumption that absolute risks were comparable, and no attempt was made to evaluate the uncertainty resulting from this choice. For most cancer sites, however, there are few quantitative

data other than those available from the LSS, and it cannot be excluded that other transfer models may be appropriate for different cancer sites (Land 1990, Land and Sinclair 1993, NCRP-126, EPA 1999). Moreover, the choice of transfer model involves considerable uncertainty. In the current report, uncertainty from this source has been evaluated, with central estimates chosen to fall in between the NIH model and a model in which relative rather than absolute risks are assumed comparable for Japanese and US populations. Cancers of the female breast, thyroid gland, and skin were treated somewhat differently, as discussed in IV.G above.

9. Biological effectiveness of different types of radiation. The 1985 NIH report considered exposure to low-LET radiation (i.e., photons) only, since this was the principal type of radiation to which the Japanese atomic-bomb survivors were exposed. The results of that study thus were not applicable to exposures to high-LET radiation, such as neutrons and alpha particles, which have a greater biological effectiveness per unit dose than low-LET radiation. The 1985 report also did not take into account that low-energy photons and electrons may have a greater biological effectiveness than the high-energy gamma rays to which the atomic-bomb survivors were exposed. In contrast, the present report considers exposures to different radiation types, including photons, electrons, alpha particles, and neutrons. The biological effectiveness of different radiations is represented by the radiation effectiveness factor (REF), which generally depends on the radiation type and its energy. For each radiation type and energy of concern, the REF is described by a probability distribution that is intended to represent uncertainties in relevant data obtained from radiobiological studies.

10. Treatment of uncertainty. The treatment of uncertainty is similar to that in the 1985 report in that uncertainties from each of several components or sources are evaluated separately and then combined into an overall assessment based on the assumption that uncertainties from different sources are independent. It is also similar in that many sources could not be evaluated using rigorous statistical procedures, but required subjective judgements of the investigators. However, the treatment of uncertainties in the updated report differs from the 1985 report in several respects. First, components of uncertainty that were not evaluated earlier have been added, including especially statistical variability in the risk coefficients and uncertainty resulting from transferring risk coefficients based on Japanese A-bomb survivors to a contemporary U.S. population. Second, uncertainty distributions were selected to reflect available data and the best judgment of the investigators, and were not limited to log-normal distributions as was the case in 1985. Third, Monte Carlo simulations were used to combine uncertainties, a feature that made flexible selection of uncertainty distributions possible. Fourth, uncertainty was not treated as an "add-on", developed after the central estimates had been determined, but rather was a fundamental part of the process. That is, emphasis was not on determining single point estimates, but on developing overall uncertainty distributions, calculated by combining the uncertainty distributions from each of the contributing sources. Given an uncertainty distribution, it is of course possible to determine medians, means, and various percentiles or credibility limits. Finally, the on-line computer software (IREP) incorporates "customized" Monte Carlo simulations to obtain the distribution of a desired AS, taking into account the exposure scenario, certain characteristics of the individual, and the specific type of cancer.

The above modifications drew heavily on developments in uncertainty analysis that have occurred since 1985. The BEIR V report used Monte Carlo simulations to evaluate statistical uncertainty in lifetime risks, but relied on lognormal propagation of errors for evaluating several other uncertainty sources. More recently, both NCRP and EPA have used Monte Carlo simulations, including flexible choice of distributions to describe uncertainties from individual sources. However, NCRP and EPA were primarily concerned with uncertainties in lifetime risks to populations rather than uncertainties in risks for individuals with specific characteristics. Furthermore, NCRP provided a distribution only for the lifetime risk of all fatal cancers, although the report contains discussion of specific cancer types. To our knowledge, the work reported here is the first to evaluate uncertainty distributions for specific AS values associated with any of a wide range of specific cancer types, individual characteristics, and exposure scenarios.

VI. Use of the AS estimates and their uncertainties for adjudication.

This report makes no recommendations regarding how the estimated assigned shares and the accompanying software IREP should be used to adjudicate claims. However, some possible applications of the 1985 tables are briefly described below. Further discussion of applications is provided by NAS-NRC (2000).

One approach is to use a sliding scale, and British Nuclear Fuels developed such a compensation scheme based on the 1985 tables (with some modifications) (Thomas et al. 1991; Wakeford, 1999). Under this scheme, persons whose estimated AS values are 50% or higher receive full awards, whereas persons whose estimates are between 20% and 50% receive graduated partial awards. This approach makes no use of uncertainties, but avoids the arbitrariness of a full award for a person with an dose that results in a PC of exactly 50%, and nothing for a person with a slightly lower dose that results in a PC of 49%.

Another approach is an "all or nothing" approach in which a full award is granted if the PC exceeds some specified value, and no award is granted if the PC is less than the specified value. When 50% is the chosen cutoff value, this approach can be considered as based on tort law in which claims are awarded if it is at least as likely as not that the cancer was caused by radiation.

CIRRPC (1988) developed a procedure for screening claims of radiation-induced cancer that made extensive use of uncertainties in the PCs that were provided in the 1985 NIH report. Under this scheme, a person passes the screening if the upper 99% confidence limit (or some other chosen level) on the estimated PC exceeds 50%. The CIRRPC report notes that:

> "This procedure is designed to insure that cases which have even a small chance of a true PC, that is 0.5 (50 percent) or greater (i.e., that meet the "as least as likely as not" criterion), are developed for assessment of causality, yet will avoid detailed development of those cases for which there is virtually no chance that the true PC would be as large as 50 percent. The screening process is not a decision-making process that should result in automatic compensation."

The DVA has subsequently used the screening doses (based on the upper 99% confidence limit) developed by CIRRPC. In practice, few cases who have passed the screening have failed to receive rewards. This policy has the advantage that is highly unlikely to exclude persons with meritorious claims. However, it is likely to award many persons whose true PCs are very much less than 50%, a use of funds that some might question. It also has the anomaly that the more uncertain the PC estimate the more likely that a claimant will be awarded. For example, as noted in the NAS review of this report (2000), a claimant with a precisely estimated PC of 44% (CI: 41%-47%) would fail to receive an award, while a claimant with an imprecisely estimated PC of 9% (CI: 0%-82%) would be awarded..

Both the sliding scale approach and the "all or nothing" approach as practiced by the DVA could be varied in many ways. For example, PCs other than 50% could be used as the basis of awards, and less stringent upper confidence limits (e.g. 90% instead of 99%) could be used. Compensation based on the years of life lost from the cancer has also been proposed and has

certain advantages (Robins and Greenland 1991).

A purely numerical consideration is that estimates obtained by Monte Carlo simulation of the 99th percentile of a probability distribution are unstable unless based on a very large sample size. For example, an estimate based on a simulated sample of size 100 is determined by the two highest values. With a sample of 1000 the estimate depends upon the highest 11 values, and for a sample of 10,000 it depends upon the largest 101 values. The estimate based on 100 simulations is obtained very quickly but is highly unstable, whereas that based on 10,000 simulations is reasonably stable but requires a longer time to calculate.

REFERENCES

Beyea J, Greenland S. The importance of specifying the underlying biologic model in estimating the probability of causation. Health Physics, 1999; 76:269-274.

Blot, W.J., Akiba, S., Kato, H. Ionizing radiation and lung cancer: A review including preliminary results from a case-control study among A-bomb survivors. In: Atomic Bomb Survivor Data: Utilization and Analysis, R.L. Prentice and D.J. Thompson, eds. Philadelphia: Society for Industrial and Applied Mathematics, pp 235-248 (1984).

Boice JD Jr., Monson RR. Breast cancer in women after repeated fluoroscopic examinations of the chest. J Natl Cancer Inst 1977; 59:823-32.

Carr ZA, Kleinerman RA, Weinstock R, Stovall M, Greim ML, Land CE. Malignant neoplasms after radiation therapy for peptic ulcer. Radiation Research 2002; 157:xx-xx.

CDC (Centers for Disease Control). Morbidity and Mortality Weekly Report, Atlanta, GA - Cigarette smoking among adults - United States 1993. JAMA 1995; 273(5):369-370.

CIRRPC (Committee on Interagency Radiation Research and Policy Coordination) Science Panel Report No. 6. Use of probability of causation by the Veterans Administration in the Adjudication of Claims of injury due to exposure to ionizing radiation. Committee on Interagency Radiation Research and Policy Coordination, Office of Science and Technology Policy, Executive Office of the President, Washington, D.C., August 1988 (ORAU 88/F-4).

Cologne JB, Tokuoka S, Beebe GW, Fukuhara T, Mabuchi K. Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. Radiat Res 152:364-73, 1999

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials, 1986; 7:177-188.

DOJ (Department of Justice). Final Report of the Radiation Exposure Compensation Act Committee, submitted to the Human Radiation Interagency Working Group, July 1996

EPA (Environmental Protection Agency). Estimating Radiogenic Cancer Risks. EPA Report 402-R-00-003, Washington, D.C., May 1999.

Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. American Journal of Epidemiology, 1988; 128:1186-1197.

Greenland S. Relation of probability of causation to relative risk and doubling dose: a methodologic error that has become a social problem. American Journal of Public Health, 1999; 89:1166-1169.

Griem ML, Kleinerman RA, Boice JD Jr, Stovall M, Shefner D, Lubin JH. Cancer following radiotherapy for peptic ulcer. J Natl Cancer Inst 1994; 86:842-849.

Grogan HA, Sinclair WK, Voilleque PG. Assessing Risks from Exposure to Plutonium. Final Report. Part of Task 3: Independent Analysis of Exposure, Dose and Health Risk to Offsite Individuals. Radiological Assessment Corporation (*RAC*) Report no. 5, Revision 2, February, 2000.

Ichimaru M, Ishimaru T, Belsky JL. Incidence of leukemia in atomic bomb survivors belonging

to a fixed cohort in Hiroshima and Nagasaki, 1950-71. Radiation dose, years after exposure, age at exposure, and type of leukemia. J Radiat Res, 1978; 19:262-282

ICRP (International Commission on Radiological Protection). 1980. Biological effects of inhaled radionuclides. ICRP Publication 31. Annals of the ICRP Vol. 4, No. 1-2. Oxford, England.

ICRP (International Commission on Radiation Protection). 1990 recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Annals of the ICRP 1991; 21 No. 1-3:1-193.

ICRP (International Commission on Radiation Protection). ICRP Publication 79. Genetic susceptibility to cancer. Ann ICRP 1998; 28:1-158.

Jacobi W, Paretzke HG, Schindel F. Lung cancer risk assessment of radon-exposed miners on the basis of a proportional hazards model. In: Proc. Int. Conf. Occupational Radiation Safety in Mining, pp. 17-24, (ed. H Stocker), Canadian Nuclear Assoc., Toronto, 1985.

Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. 7. Mortality, 1950-1978: Part 1. Cancer mortality. Radiat Res 1982; 90:395-432.

Kellerer AM, Nekolla E. Neutron versus gamma-ray risk estimates. Inferences from the cancer incidence and mortality data in Hiroshima. Radiat Environ Biophys 1997; 36:73-83.

Kerr GD. Organ dose estimates for the Japanese atomic bomb survivors. Health Phys 1979; 37:487-508

Kocher, D.C., Apostoaei, A.I., and Hoffman, F.O. 2002. "Radiation Effectiveness Factors (REFs) for Use in Calculating Probability of Causation of Radiogenic Cancers," report prepared for National Institute of Occupational Safety and Health, SENES Oak Ridge, Inc., Oak Ridge, Tennessee (in preparation).

Land CE, Boice JD Jr, Shore RE, Norman JE, Tokunaga M. Breast cancer risk from low-dose exposures to ionizing radiation: results of a parallel analysis of three exposed populations of women. J Natl Cancer Inst 1980;65:353-75.

Land CE. Carcinogenic effect of radiation on the human digestive tract and other organs. In: Upton AC, Albert RE, Burns F, Shore RE, eds. Radiation carcinogenesis. New York: Elsevier/North Holland, 1986;347-378.

Land CE. Projection of risk from one population to another. In: Renz K, ed. Risk estimates for radiation carcinogenesis. Köln: Institut für Strahlenschutz der Berufsgenossenschaft der Feinmechanik und Elektotechnik und der Berufsgenossenschaft der chemischen Industrie, 1990;42-49.

Land CE, Sinclair WK. The relative contributions of different cancer sites to the overall detriment associated with low-dose radiation exposure. Ann ICRP 1991;22:31-57.

Land CE, Hayakawa N, Machado S, Yamada Y, Pike MC, Akiba A, Tokunaga M. A case-control interview study of breast cancer among Japanese A-bomb survivors: II. Interactions between epidemiological factors and radiation dose. Cancer Causes Control 1994;5:167-76.

Little MP, Boice JD Jr. Comparison of breast cancer incidence in the Massachusetts tuberculosis

fluoroscopy cohort and in the Japanese atomic bomb survivors. Radiat Res 1999;151:280-292.

Lubin JH, Steindorf K. Cigarette use and the estimation of lung cancer attributable to radon in the United States. Radiat Res. 1995; 141:79-85.

Mabuchi K, Soda M, Ron E, Tokunaga M, Ochiubo S, Sugimoto S, Ikeda T, Terasaki M, Preston DL, Thompson DE. Cancer incidence in atomic bomb survivors. Part I: Use of the tumor registries in Hiroshima and Nagasaki for incidence studies. Radiat Res 1994; 137:S1-S16.

Mattson A, Holmberg E, Preston D, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Manuscript included among original papers included in the doctoral thesis of Anders Mattson, "On Ionizing Radiation and Breast Cancer Risk," presented to the faculty of the Karolinska Institute, Stockholm, Sweden, 1999.

Mays CW, Spiess H. Epidemiological studies of German patients injected with Ra-224. In: Epidemiology Applied to Health Phys. Proceedings of the 16th Midyear Topical Meeting of the Health Physics Society, Albuquerque, N.M.: National Technical Information Service, Springfield, VA, 1983, CONF-830101; 159-166

NAS/NRC 1980. National Academy of Sciences/National Research Council, Committee on the Biological Effects of Ionizing Radiation: The effects on populations of exposure to low levels of ionizing radiation: 1980, BEIR III). National Academy Press, Washington, D.C.

NAS/NRC 1984. Oversight Committee on Radiodepidemiological Tables. Assigned Share for Radiation as a Cause of Cancer - Review of Radioepidemiological Tables Assigning Probabilities of Causation (Final Report). National Academy Press, Washington, D.C., 1984.

NAS/NRC 1988. National Academy of Sciences/National Research Council, Committee on Health Effects of Exposure to Radon. Health Effects of Exposure to Radon and Other Internally-Deposited Alpha Emitters: BEIR IV. National Academy Press, Washington, D.C., 1988.

NAS/NRC 1990. National Academy of Sciences/National Research Council, Committee on the Biological Effects of Ionizing Radiation: The effects on populations of exposure to low levels of ionizing radiation: 1990, BEIR V. National Academy Press, Washington, D.C.

NAS/NRC 1998. Report of the Committee on Health Effects of Exposure to Low Levels of Ionizing Radiations (BEIR VII) Phase I. Health Effect of Exposure to Low Levels of Ionizing Radiation. Time for Reassessment? National Academy Press, Washington, D.C., 1998, 76 pp.

NAS/NRC 1999. National Academy of Sciences/National Research Council, Committee on Health Effects of Exposure to Radon. Health Effects of Exposure to Radon: BEIR VI. National Academy Press, Washington, D.C., 1999.

NAS/NRC 2000. Committee on an Assessment of Centers for Disease Control and Preventiion Radiation Studies from DOE Contractor Sites: Subcommittee to Review the Radioepidemiology Tables. A Review of the Draft Report of the NCI-CDC Working Group to Revise the "1985 Radioepidemiological Tables." National Research Council, Board on Radiation Effects Research, 2101 Constitution Avenue, NW, Washington, DC 20418, 2000, 75 pp.

NAS/NRC 2001. Committee on Dosimetry for the Radiation Effects Foundation, Board on Radiation Effects, Division on Earth and Life Sciences, National Research Council. Status of the Dosimetry for the Radiation Effects Research Foundation (DS86). National Academy Press,

Washington, D.C., 2001, 198 pp.

National Center for Health Statistics, "Cigarette smoking and Health Care Characteristics, U.S., July 1964-June 1965." Series 10, No. 34, U.S. Department of Health Education and Welfare, Washington, D.C., 1967.

NCRP (National Council on Radiation Protection and Measurements). Influence of dose and its distribution in time on dose-response relationships for low-LET radiation. NCRP Report No. 64. National Council on Radiation Protection and Measurements, Bethesda, MD, 1980.

NCRP (National Council on Radiation Protection and Measurements), 1990. The relative biological effectiveness of radiations of different quality. NCRP Report No. 104. Bethesda, Maryland

NCRP (National Council on Radiation Protection and Measurements). Risk estimates for radiation protection. National Council on Radiation Protection and Measurement, Washington, D.C., 1993, NCRP Report No. 115, 148 pp.

NCRP (National Council on Radiation Protection and Measurements). A guide for uncertainty analysis in dose and risk assessments related to environmental contamination. NCRP Commentary No. 14. National Council on Radiation Protection and Measurements, Bethesda, MD, 1996.

NCRP (National Council on Radiation Protection and Measurements). Uncertainties in fatal cancer risk estimates used in radiation protection. NCRP Report No. 126. National Council on Radiation Protection and Measurements, Bethesda, MD, 1997.

Nekolla EA, Kreisheimer M, Kellerer AM, Kuse-Isingschulte M, Gossner W, Spiess H. Induction of malignant bone tumors in radium-224 patients: risk estimates based on the improved dosimetry. Radiat Res 2000; 153:93-103.

NIH (National Institutes of Health). Rall JE, Beebe GW, Hoel DG, Jablon S, Land CE, Nygaard OF, Upton AC, Yalow RS, Zeve VH. Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables. National Institutes of Health, Bethesda, Maryland, 1985;355 pp.

Parker LN, Belsky JL, Yamamoto T, Kawamoto S, Keehn RJ. Thyroid carcinoma after exposure to atomic radiation. A continuing survey of a fixed population, Hiroshima and Nagasaki, 1958-1971. Technical Report 5-73. Radiation Effects Research Foundation, Hiroshima, 1973.

Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds (1997) Cancer Incidence in Five Continents, Vol VII (IARC Scientific Publications No. 143), Lyon, IARC.

Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 1990; 123: 275-284.

Pierce DA, Preston DL. Joint analysis of site-specific cancer risks for the atomic bomb survivors. Radiat Res 1993; 134:134-142.

Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the Mortality of Atomic Bomb Survivors. Report 12, Part I. Cancer: 1950-1990. Radiat Res 1996; 146:1-27

Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. Radiat Res 2000;154:178-86.

Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical Recipes in FORTRAN 77. The Art of Scientific Computing. Second Edition. Volume 1 of FORTRAN Numerical Recipes. Cambridge University Press. 1996

Preston DL, Kusumi S, Tomonaga M, Izumu S, Ron E, Kuramoto A, Kamata N, Dohy H, Matsui T, Nonaka H, Thompson DE, Soda M, Mabuchi K. Cancer incidence in atomic bomb survivors, Part III: Leukemia, lymphoma, and multiple myeloma, 1950–87. Radiat Res. 1994; 137:S68-S97.

Preston DL, Lubin JH, Pierce DA: Epicure Users Guide. Seattle, Hirosoft International, 1991

Puskin JS, Nelson CB. Estimates of radiogenic cancer risks. Health Phys 1995; 69: 93-101.

Robins JM, Greenland S. Estimability and estimation of excess and etiologic fractions. Statistics in Medicine, 1989; 8:845-859.

Robins JM, Greenland S. The probability of causation under a stochastic model for individual risks. Biometrics, 1989; 45:1125-1138.

Robins J, Greenland S. Estimatibility and estimation of expected years of life lost due to a hazardous exposure. Stat Med 10: 79-93, 1991.

Roesch WC, Ed., US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report (2 vols., Radiation Effects Research Foundation, Hiroshima, 1987).

Rogot, E., Murray, J.L. Smoking and causes of death among U.S. veterans: 16 years of *observation. Public Health Rep. 95:213-222 (1980).*

Ron E, Modan B. Benign and malignant thyroid neoplasms after childhood irradiation for tinea capitis. JNCI 1980; 65:7-11

Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD, Jr. Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. Radiat Res 1995; 141:259-277.

Ron E, Preston DL, Kishikawa M, Kobuke T, Iseki M, Tokuoka S, Tokunaga M, Mabuchi K. Skin tumor risk among atomic-bomb survivors in Japan. Cancer Causes and Control 1998; 9:393-401.

Scotto J, Fears T, Fraumeni JF Jr. Incidence of nonmelanoma skin cancer in the United States. In: U.S. Dept. Health and Human Services: 113 pp. Vol NIH Publ. No. 83-2433, 1983.

SEER 1973-1981 SEER Cancer Statistics Review, 1973-1981, National Cancer Institute. NIH Pub. No. 84-xxxx.. Bethesda, MD, 1984.

SEER 1973-1994. Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK (eds). SEER Cancer Statistics Review, 1973-1994, National Cancer Institute. NIH Pub. No. 97-2789. Bethesda, MD, 1997.

Shore RE, Hempleman LH, Kowluk E, Mansur PS, Pasternack BS, Albert RE, Haughie EG.

Breast neoplasms in women treated with x rays fro acute postpartum mastitis. J Natl Cancer Inst 1977; 59:813-22.

Shore RE, Moseson M, Xue X, Tse Y, Harley N, Pasternack BS. Skin cancer after x-ray treatment for scalp ringworm. Radiat. Res. 2002; 157:410-8.

Smith PG, Doll R. Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays. Br Med J 1982; 284:449-460

Thomas DI, Salmon L, Antell BA. Revised technical basis for the BNFL/UKAEA compensation agreement for radiation linked diseases. J Radiol Prot 11:111-116, 1991.

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, Preston DL. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res. 1994; 137:S17-S67.

Tokunaga M, Land CE, Yamamoto T, Asano M, Tokuoka S, Ezaki H, Nishimori I. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1980. Radiat Res 1987;112:243-273.

UNSCEAR 1988. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, Effects and Risks of Ionizing Radiation, No. E.88.IX.7, United Nations, New York.

UNSCEAR 1993. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, Effects and Risks of Ionizing Radiation, No. E.94.IX.2, United Nations, New York.

UNSCEAR 1994. United Nations Scientific Committee on the Effects of Atomic Radiation. Annex A: Epidemiological Studies of Radiation Carcinogenesis, pages 11-183 in Sources, Effects and Risks of Ionizing Radiation, No. E.94.IX.11. United Nations, New York.

Wakeford R, Antell BA, Leigh WJ. A review of probability of causation and its use in a compensation scheme for nuclear industry workers in the United Kingdom. Health Phys 1998; 74:1-9.

APPENDIX A: Text of Congressional Mandate and Excerpt from Presidential Statement

Public Law 97-414 - January 4, 1983

"7(b)(1) Within one year after the date of enactment of this Act, the Secretary of Health and Human Services shall devise and publish radio-epidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses. These tables shall show a probability of causation of developing each radiation related cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to the onset of the cancer in question, and such other categories as the Secretary, after consulting with appropriate scientific experts, determines to be relevant. Each probability of causation shall be calculated and displayed as a single percentage figure.

(2) At the time the Secretary of Health and Human Services publishes the tables pursuant to paragraph (1), such Secretary shall also publish--

> (A) for the tables of each radiation related cancer, an evaluation which will assess the credibility, validity, and degree of certainty associated with such tables; and
>
> (B) a compilation of the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation related cancer and has received any given dose.

(3) The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever he deems it necessary to insure that they continue to represent the best available scientific data and expertise."

Excerpt from President Reagan's statement on the occasion of his signing the Orphan Drug Act.

> ". . . there is as yet no consensus among radiation experts in relating human cancers and exposure to low levels of radiation. Yet, Section 7 mandates that probability of causation tables be calculated for even very small dose levels. Accordingly, I am directing the Secretary of Health and Human Services to complete the tables to the extent that may be possible and scientifically responsible, in light of the analysis also mandated by Section 7, which requires him to 'assess the credibility, validity, and degree of uncertainty associated with such tables.'"

APPENDIX B: DHHS Charter - Ad Hoc Working Group to Develop Radioepidemiological Tables

"Purpose

Section 7(b) of Public Law 97-414 directs the Secretary of Health and Human Services to devise and publish radioepidemiological tables that estimate the likelihood that persons with any radiation-related cancer who received specific radiation doses before the onset of the cancer developed the disease as a result of such exposure. The tables must show the probability of causation for each cancer associated with receipt of doses ranging from 1 millirad to 1,000 rads in terms of sex, age at time of exposure, time from exposure to disease onset, and such other categories as the Secretary, after consultation with appropriate scientific experts, determines to be relevant. In carrying out this mandate, the Secretary deems it necessary to establish an Ad Hoc Working Group to Develop Radioepidemiological Tables comprised of scientific experts whose qualifications will insure a thorough, competent and timely completion of the task.

"Authority

42 U.S. Code 217a, Section 222 of the Public Health Service Act, as amended.

This Ad Hoc Working Group to Develop Radioepidemiological Tables is governed by the provisions of Public Law 902-463, which sets forth standards for the formation and use of advisory committees.

"Function

In addition to developing radioepidemiological tables, the Ad Hoc Working Group shall:

7. Assess the credibility, validity, and degree of certainty associated with such tables; and

8. Compile the formulas that yielded the probabilities of causation listed in such tables. Such formulas shall be published in such a manner and together with information necessary to determine the probability of causation of any individual who has or has had a radiation-related cancer and has received any given dose.

The tables specified in paragraph (1) and the formulas specified in paragraph (2) shall be devised from the best available data that are most applicable to the United States, and shall be devised in accordance with the best available scientific procedures and expertise. The Secretary of Health and Human Services shall update these tables and formulas every four years, or whenever necessary, to insure that they continue to represent the best available scientific data and expertise.

"Structure

The Ad Hoc Working Group to Develop Radioepidemiological Tables shall consist of eight members, including the chairperson. Members and chair- person shall be selected by the Secretary, or designee, from outstanding authorities in the fields of endocrinology, radiation